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NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
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NEWS 11	Jun 10	PCTFULL has been reloaded
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NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
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NEWS 18	Aug 08	NTIS has been reloaded and enhanced
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NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 28	Oct 21	EVENTLINE has been reloaded
NEWS 29	Oct 24	BEILSTEIN adds new search fields
NEWS 30	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 31	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 32	Nov 18	DKILIT has been renamed APOLLIT
NEWS 33	Nov 25	More calculated properties added to REGISTRY
NEWS 34	Dec 02	TIBKAT will be removed from STN
NEWS 35	Dec 04	CSA files on STN

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L1      74620 HSP## OR (HEAT(W) SHOCK(W)(PROTEIN# OR PEPTIDE#))

=> s (NK or (natural(w)killer))(w)cell#
   3 FILES SEARCHED...
L2      83305 (NK OR (NATURAL(W) KILLER))(W) CELL#

=> s l1 and l2
L3        298 L1 AND L2

=> s l3 and activat?
L4         92 L3 AND ACTIVAT?

=> s l4 and py<2000
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L5         57 L4 AND PY<2000

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L6          24 DUP REM L5 (33 DUPLICATES REMOVED)

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L6 ANSWER 1 OF 24 BIOTECHDS COPYRIGHT 2002 THOMSON DERWENT AND ISI
ACCESSION NUMBER: 1999-15111 BIOTECHDS
TITLE: **Activation** of **natural killer cells** to stimulate immune response, especially in treatment of tumors, infections and autoimmune diseases; recombinant **heat shock protein** or partial protein, used to induce **natural killer cell activation** or stimulation, in tumor, infectious disease and autoimmune disease therapy
AUTHOR: Multhoff G
PATENT ASSIGNEE: Multhoff G
LOCATION: Munich, Germany.
PATENT INFO: DE 19813760 **7 Oct 1999**
APPLICATION INFO: DE 1998-1013760 27 Mar 1998
PRIORITY INFO: DE 1998-1013760 27 Mar 1998
DOCUMENT TYPE: Patent
LANGUAGE: German
OTHER SOURCE: WPI: 1999-552201 [47]
AN 1999-15111 BIOTECHDS
AB A **heat shock protein** (I), specifically **Hsp70** or a protein at least 70%, preferably 80%, identical to the C-terminal region of **Hsp70**, is claimed. It can be used to **activate natural killer cells** (NKC). (I) is used to induce an immune response and to **activate** or stimulate NKC proliferation. It can also be used to increase NKC cytolytic activity against human or animal cells that express **Hsp70**, particularly tumor cells or cells from patients with bacterium, fungus or virus infections, or autoimmune diseases. The **heat shock protein** is preferably administered in the presence of a cytokine, especially an interleukin, particularly interleukin-2, interleukin-12 or interleukin-15. The NKC preferably expresses CD16, is stimulated by interleukin-2, does not express CD3, does not have alpha-beta or gamma-delta T-lymphocyte receptors, or is not dependent on the major histocompatibility complex of the patient. A pharmaceutical composition containing 10-1,000 ug/ml (I), and NKC **activated** by (I) can be used for tumor, infectious disease and autoimmune disease therapy. (I) can be recombinant, and preferably contains at least bases 348-641 or 384-561 of the C-terminal region of **Hsp70**. (16pp)

L6 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:640719 CAPLUS
DOCUMENT NUMBER: 131:252569
TITLE: **Hsp70** protein **activation** of **NK cells** in treatment of cancers, infections and autoimmune diseases
INVENTOR(S): Multhoff, Gabriele
PATENT ASSIGNEE(S): Germany
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9949881	A2	19991007	WO 1999-EP2165	19990329 <--
WO 9949881	A3	19991223		
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19813760	A1	19991007	DE 1998-19813760	19980327 <--
CA 2325735	AA	19991007	CA 1999-2325735	19990329 <--

EP 1066050 A2 20010110 EP 1999-913314 19990329
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, LI, LU, NL, SE, MC, PT, IE, FI
PRIORITY APPLN. INFO.: DE 1998-19813760 A 19980327
WO 1999-EP2056 A 19990326
WO 1999-EP2165 W 19990329

AB The invention relates to the use of **Hsp70** protein or fragments thereof to **activate NK cells** and to pharmaceuticals, medicinal products or medicinal adjuvants contg. an **Hsp70** protein or fragments thereof or **activated NK cells**. The invention also relates to a method for **activating NK cells** and the medical applications of the products obtained through the inventive method. Thus, **NK cells** preactivated with **Hsp70** inhibited growth and metastasis of **Hsp70**-producing tumor cells in scid mice.

L6 ANSWER 3 OF 24 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000070787 MEDLINE
DOCUMENT NUMBER: 20070787 PubMed ID: 10602674
TITLE: Expression and role of **heat-shock protein** 65 (**HSP65**) in macrophages during Trypanosoma cruzi infection: involvement of **HSP65** in prevention of apoptosis of macrophages.
AUTHOR: Sakai T; Hisaeda H; Ishikawa H; Maekawa Y; Zhang M; Nakao Y; Takeuchi T; Matsumoto K; Good R A; Himeno K
CORPORATE SOURCE: Department of Parasitology and Immunology, The University of Tokushima School of Medicine, Tokushima, Japan.
SOURCE: Microbes Infect, **(1999 May)** 1 (6) 419-27.
Journal code: 100883508. ISSN: 1286-4579.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000616

AB The 65-kDa **heat-shock protein** (**HSP65**) is thought to play a role in host defense against infections with various microbial pathogens and in autoimmune inflammatory disorders. We investigated the biological function and expression mechanism of **HSP65** in macrophages of mice infected with Trypanosoma cruzi. BALB/c mice, which are susceptible to T. cruzi, showed high levels of parasitemia, and 80% of these mice died within 42 days after the infection, whereas resistant C57BL/6 or DBA/2 mice showed low levels of transient parasitemia and all survived. **HSP65** expression was correlated with resistance to T. cruzi infection; **HSP65** was more strongly expressed in macrophages of resistant C57BL/6 and DBA/2 mice than in macrophages of susceptible BALB/c mice. Immunodeficient BALB/c-nu/nu (nude) and C.B-17 scid/scid (SCID) mice were shown to be highly susceptible to this infection, and they did not express detectable levels of **HSP65**, suggesting that T cells play essential roles in the expression of **HSP65** as well as in protective immunity against the infection. CD4(+) T cells, but not CD8(+) T cells or gammadelta T cells, were the cell population responsible for the induction of **HSP65** expression in macrophages. Furthermore, depletion of asialo GM-1(+) **NK cells** made resistant C57BL/6 mice more susceptible to the infection, and **HSP65** expression in their macrophages was abolished. Semiquantitative reverse transcription PCR analyses showed that both interferon gamma (IFN-gamma) and tumor necrosis factor alpha (TNF-alpha) mRNA levels in CD4(+) T cells became low when resistant C57BL/6 mice were depleted of **NK cells**, suggesting that **NK cells** contribute to functional differentiation of CD4(+) T cells and thereby affect the induction of **HSP65** expression. To determine the function of **HSP65**,

macrophages were treated in vitro with antisense oligonucleotide for **HSP65** prior to inducing **HSP65** with IFN-gamma plus TNF-alpha or T. cruzi infection. This treatment did not affect the production of nitric oxide following **activation**, but the treated macrophages became susceptible to apoptosis. These results indicate that **HSP65** plays a role in preventing the apoptosis of macrophages and thereby contributes to host resistance against T. cruzi infection.

L6 ANSWER 4 OF 24 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999123776 MEDLINE
DOCUMENT NUMBER: 99123776 PubMed ID: 9924701
TITLE: **Heat shock protein** antibodies in sarcoma patients undergoing 41.8 degrees C whole body hyperthermia.
AUTHOR: Katschinski D M; Benndorf R; Wiedemann G J; Mulkerin D L; Touhidi R; Robins H I
CORPORATE SOURCE: University of Wisconsin, School of Medicine, Madison, USA.
SOURCE: JOURNAL OF IMMUNOTHERAPY, **(1999 Jan)** 22 (1) 67-70.
Journal code: 9706083. ISSN: 1524-9557.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990402
Last Updated on STN: 19990402
Entered Medline: 19990325

AB Previous in vitro studies of sarcoma and normal cell lines exposed to 41.8 degrees C (x 60 min) demonstrated selective increased expression of members of the **heat shock protein** (**HSP**) family 70 on the cell surface of the sarcoma cells only. One implication of these data relates to the clinical application of targeting a stress-inducible, tumor-specific immune response. We therefore elected to measure immune response parameters (i.e., serum antibodies against HSP70i, 60, and 27) in six patients with sarcoma using a Western blot technique. These study patients received one to four successive 41.8 degrees C whole-body hyperthermia (WBH) x 60-min treatments (given every 3 weeks). We also tested the serum of 10 untreated healthy control subjects for the same parameters. In all patients, baseline **HSP** antibody levels were detectable; in no case did WBH result in an increase in **HSP** antibodies. The serum of one patient with sarcoma demonstrated a strong nonfluctuating reaction against **HSP27** before and after WBH that had no obvious correlation; this was not observed in the sera of the control subjects. This study suggests that WBH does not induce a B-cell response to **HSP** family 70 antigens; these data, however, do not exclude the possibility of **NK cell activation** due to **HSP** antigen presentation.

L6 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:260869 CAPLUS
DOCUMENT NUMBER: 133:265295
TITLE: Immune surveillance in the gut
AUTHOR(S): Duchmann, R.
CORPORATE SOURCE: Innere Medizin II Medizinische Klinik und Poliklinik Universitat des Saarlandes, Homburg, D-66424, Germany
SOURCE: Falk Symposium (**1999**), 109(Colorectal Cancer), 38-47
CODEN: FASYDI; ISSN: 0161-5580
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 30 refs. is presented regarding the general features of the

intestinal immune system, as well as candidate antigens and immune cells for which there are indications that they mediate immunity to colorectal cancer. Discussed are: the intestinal immune system; host defense factors in the intestinal mucosa; role of .gamma..delta. T cells; role of **heat-shock proteins**; role of cytolytic T-lymphocytes; role of **natural killer cells**; and role of Fas-mediated apoptosis. Contrary to the prediction of the immune surveillance hypothesis, the increased frequency of cancers in renal transplant recipients is not generalized but is confined to particular types such as non-Hodgkin's lymphoma, squamous carcinoma of the skin, melanoma, Kaposi's sarcoma, liver cancer, and cervical cancer. Patients with primary immunodeficiency disorders show a predominance of lymphomas but no increase in colorectal carcinoma. Immune surveillance as a screening mechanism to prevent or eradicate early colorectal carcinoma has not been formally established. Anti-tumor immune responses are countered by colorectal carcinoma cells as they develop a variety of immune-escape mechanisms. Identification of shared colorectal carcinoma epitopes and development of immunization protocols which ensure effective **activation** of appropriate T cell effector populations may exploit the concept of immune surveillance for prevention of colorectal carcinoma and generate new therapies for treatment of established carcinoma.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:165842 CAPLUS
DOCUMENT NUMBER: 133:87727
TITLE: Reduced aldehyde dehydrogenase levels in the brain of patients with Down syndrome
AUTHOR(S): Lubec, G.; Labudova, O.; Cairns, N.; Berndt, P.; Langen, H.; Fountoulakis, M.
CORPORATE SOURCE: Department of Pediatrics, University of Vienna, Vienna, Austria
SOURCE: Journal of Neural Transmission, Supplement (**1999**), 57(Molecular Biology of Down Syndrome), 21-40
CODEN: JNTSD4; ISSN: 0303-6995
PUBLISHER: Springer-Verlag Wien
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aldehyde dehydrogenase (ALDH) is a key enzyme in fructose, acetaldehyde and oxalate metab. and represents a major detoxification system for reactive carbonyls and aldehydes. In the brain, ALDH exerts a major function in the metab. of biogenic aldehydes, norepinephrine, dopamine and diamines and .gamma.-aminobutyric acid. Subtractive hybridization studies in Down Syndrome (DS) fetal brain showed that mRNA for ALDH are downregulated. Here we studied the protein levels in the brain of adult patients. The proteins from five brain regions of 9 aged patients with DS and 9 controls were analyzed by two-dimensional (2-D) gel electrophoresis and identified by matrix-assisted laser desorption ionization mass spectrometry. ALDH levels were reduced in the brain regions of at least half of the patients with Down Syndrome, as compared to controls. The decreased ALDH levels in the DS brain may result in accumulation of aldehydes which can lead to the formation of plaques and tangles reflecting abnormally cross-linked, insol. and modified proteins, found in aged DS brain. Furthermore, we constructed a 2-D map including approx. 120 identified human brain proteins.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 24 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999164014 MEDLINE
DOCUMENT NUMBER: 99164014 PubMed ID: 10066131
TITLE: Cold exposure and immune function.
AUTHOR: Shephard R J; Shek P N

CORPORATE SOURCE: Faculty of Physical Education and Health, Department of Public Health Sciences, University of Toronto, Ontario, Canada.. royjshep@mountain-inter.net
SOURCE: CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, **(1998 Sep)** 76 (9) 828-36. Ref: 77
Journal code: 0372712. ISSN: 0008-4212.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990429

AB The influence of cold exposure on immune function is reviewed. Data obtained mainly on small mammals suggest that the acute effect of severe chilling is a suppression of several cellular and humoral components of the immune response, including a decrease of lymphocyte proliferation, a down-regulation of the immune cascade, a reduction of natural killer (**NK**) **cell** count, cytolytic activity, **activation** of complement, and the induction of **heat shock proteins**. However, adaptation to a given cold stimulus appears to develop over the course of 2-3 weeks. Further work is needed to examine interactions between cold exposure and exercise, and to determine whether the disturbances of immune response are sufficient to impair immunosurveillance in human subjects.

L6 ANSWER 8 OF 24 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999096156 MEDLINE
DOCUMENT NUMBER: 99096156 PubMed ID: 9881829
TITLE: **Natural killer cell** reactivity: **activation** and cytolysis mechanism models, involving **heat shock protein**, haemopoietic histocompatibility, major histocompatibility complex and complement molecules.
AUTHOR: Manzo G
SOURCE: MEDICAL HYPOTHESES, **(1998 Jul)** 51 (1) 5-9. Ref: 30
Journal code: 7505668. ISSN: 0306-9877.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990402
Last Updated on STN: 19990402
Entered Medline: 19990322

AB The close association of **heat shock protein** (**HSP**), haemopoietic histocompatibility (Hh), major histocompatibility complex (MHC), and complement genes on the same chromosomal region, and the fact that all these genes are inherited on the whole in each haplotype of an individual, might indicate some evolutionary and functional correlations among them. Several data suggest for **HSP70** molecules a possible role as a molecular target recognizable by natural killer (**NK**) **cells**. **HSP70** sequences from both prokaryotic and eukaryotic organisms reveal that about half of the amino acid residues are identical and many of the remaining residues are similar. I here assume that NK reactivity might start, early in the immunogenesis process, as a effect of the interaction between **HSP70** molecules and a hypothetical **HSP** receptor of yet immature non-cytolytic **NK cells**. To this receptor, an

HSP molecule might act as an **activator** or an inhibitor depending on whether its amino acid residues are reactive or not with it, respectively. Later in the immunogenesis process, murine Hh or human equivalent molecules, dominantly expressed in bone marrow target cells, might select the non-reactive NK clones of an individual, inducing them to mature and express a lytic machinery. As a consequence of the NK maturation, proliferating hemopoietic target cells expressing only or mainly **activator HSPs** on their surface might undergo NK cytolysis. This might explain the NK lysis of apparently normal cells found in human foetal marrow; moreover, this might explain in some way the F1 hybrid resistance phenomenon. The NK reactivity of an individual would be further modulated by the expression on the NK surface of particular receptors (CD94, p58) specific for defined MHC molecules (Cw1, Cw3, Bw6, B7) on the target cells. Such a specific interaction would induce an 'NK effector inhibition'. The NK reactivity mechanism might have been further evolutionarily modified and adapted by the involvement of other NK receptors, such as CD11b (specific for the C3b factor of the complement) and CD16 (specific for the IgG Fc piece).Cooperation among **HSP**, MHC, CD11b, CD16, C3b and Fc allows us to propose original models of the **activation** and cytolysis mechanisms in the NK cytotoxicity and antibody-dependent cell cytotoxicity phenomena.

L6 ANSWER 9 OF 24 MEDLINE DUPLICATE 5

ACCESSION NUMBER: 1998052205 MEDLINE
DOCUMENT NUMBER: 98052205 PubMed ID: 9392312
TITLE: Immunosuppression by D-isomers of HLA class I heavy chain (amino acid 75 to 84)-derived peptides is independent of binding to HSC70.
AUTHOR: Woo J; Iyer S; Cornejo M C; Gao L; Cuturi C; Soulillou J P; Buelow R
CORPORATE SOURCE: SangStat Medical Corporation, Menlo Park, California 94025, USA.
SOURCE: TRANSPLANTATION, **(1997 Nov 27)** 64 (10) 1460-7.
Journal code: 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980116
Last Updated on STN: 19980116
Entered Medline: 19971230

AB BACKGROUND: Peptides derived from the class I heavy chain were shown to modulate immune responses in vitro and in vivo. A peptide derived from HLA-B2702 (2702.75-84) inhibited differentiation of cytotoxic T cells as well as T cell and **natural killer cell** -mediated cytotoxicity in vitro. Peptide-mediated immunomodulation seemed to be independent of the MHC proteins expressed by responder and stimulator cells. In vivo studies in rodents demonstrated prolongation of heart and skin allograft survival after peptide therapy. Here, the correlation between the peptide's biological activity and its amino acid sequence was analyzed using peptides derived from amino acid 75-84 of several mouse, rat, and human MHC class I proteins as well as peptides with single amino acid substitutions in the 2702.75-84 sequence. METHODS: Peptides consisting of both L- and D-amino acids were tested for inhibition of murine and human T cell-mediated and lymphokine-**activated** killer cell-mediated cytotoxicity, binding to hsc70, and prolongation of heart allograft survival in vivo. RESULTS: Replacement of glutamic acid residue (E) at position 75 with valine (V) resulted in a peptide [2702.75-84(E>V)] with increased in vitro and in vivo activity but unchanged affinity for hsc70. Surprisingly, both L- and D-isomers of 2702.75-84 and 2702.75-84(E>V) inhibited cytotoxic cells in vitro and prolonged heart allograft survival in vivo. However, as expected, the peptides consisting of D-amino acids did not bind to hsc70. CONCLUSION: Assuming that both D- and L-isomers modulate immune responses by similar

mechanisms, these results suggest that the peptides' effect is independent of binding to hsc70.

L6 ANSWER 10 OF 24 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97309764 MEDLINE
DOCUMENT NUMBER: 97309764 PubMed ID: 9167175
TITLE: Effect of hyperthermia on expression of histocompatibility antigens and **heat-shock protein** molecules on three human ocular melanoma cell lines.
AUTHOR: Blom D J; De Waard-Siebinga I; Apte R S; Luyten G P; Niederkorn J Y; Jager M J
CORPORATE SOURCE: University Hospital Rotterdam, The Netherlands.
SOURCE: MELANOMA RESEARCH, **(1997 Apr)** 7 (2) 103-9.
Journal code: 9109623. ISSN: 0960-8931.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970724
Last Updated on STN: 19970724
Entered Medline: 19970714

AB Hyperthermia is used as a new treatment modality for ocular melanoma. We wondered whether this treatment would affect the antigenicity of melanoma cells and studied the effect of hyperthermia on the expression of histocompatibility antigens (HLA), beta 2-microglobulin, as well as **heat-shock proteins** (**HSP**-60 and **HSP**-70) on choroidal melanoma cells. Uveal melanoma cell lines were exposed to different temperatures (39-45 degrees C) in a waterbath. Antigen expression was determined with fluorescence-**activated** cell sorting analysis, using monoclonal antibodies against HLA and **HSP**. In a 51Cr-release cytotoxicity assay we studied the effect of heat on natural killer (**NK**) **cell** susceptibility. Exposure to 45 degrees C for 30 min reduced expression of HLA class I antigens and beta 2-microglobulin. A greater reduction was observed after longer exposure times. Expression of **HSP**-70 was increased after exposure to 45 degrees C at all time intervals, while expression of **HSP**-60 was not induced by heat treatment. We did not find a significant difference in the **NK cell** susceptibility between heated and unheated cells. Hyperthermia has a time- and temperature-dependent effect on expression of HLA class I and **HSP** -70 molecules on the cell surface of uveal melanoma cells. Hyperthermia did not alter the susceptibility to **NK cell** lysis.

L6 ANSWER 11 OF 24 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 96178427 MEDLINE
DOCUMENT NUMBER: 96178427 PubMed ID: 8598315
TITLE: Noncytotoxic alkyl-lysophospholipid treatment increases sensitivity of leukemic K562 cells to lysis by natural killer (**NK**) **cells**.
COMMENT: Erratum in: Int J Cancer 1996 May 29;66(5):713
AUTHOR: Botzler C; Kolb H J; Issels R D; Multhoff G
CORPORATE SOURCE: GSF-Forschungszentrum fur Umwelt und Gesundheit GmbH, Institut fur Klinische Hamatologie, Munich, Germany.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, **(1996 Mar 1)** 65 (5) 633-8.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 19960506
Last Updated on STN: 19980206
Entered Medline: 19960423

AB Alkyl-lysophospholipids (ALP) are a group of anti-cancer compounds tha t have previously been shown to have the unique feature of being selectively toxic to neoplastic tissues. Because alkyl-lysophospholipids target the cell membrane as their site of action, our aim was to analyse the immunological effects of a nonlethal ALP treatment on leukemic K562 cells. In this in vitro study we used ET-18-OCH3, one of the most potent ALP derivatives, at different concentrations ranging from 25 up to 100 microgram/ml. By measurement of cell viability and of apoptosis, we determined a concentration of 25 microgram/ml ET-18-OCH3 and an incubation period of 2 hr as nonlethal for K562 cells; higher concentrations markedly reduced cell viability and led to induction of apoptosis. Similar to the effects induced by nonlethal heat shock, a nontoxic ET-18-OCH3 treatment led to a significant increase in the sensitivity of K562 cells to lysis by interleukin-2 (IL-2) stimulated natural killer (**NK**) **cells**. With respect to these results, we investigated the influence of nonlethal ALP treatment on the cell surface expression patterns and compared it to the results obtained with nonlethal heat shock. ALP treatment does not induce major histocompatibility complex (MHC) expression; however, a significant increase in the cell surface expression of **HSP72** was shown by immunoblot analysis of membrane lysates of either untreated or ET-18-OCH3 treated K562 cells. The increased sensitivity of ET-18-OCH3 treated K562 cells to lysis by **NK cells** could be correlated with the elevated cell surface expression of **HSP72**.

L6 ANSWER 12 OF 24 LIFESCI COPYRIGHT 2002 CSA
ACCESSION NUMBER: 96:75695 LIFESCI
TITLE: Recruitment of tyrosine phosphatase HCP by the killer cell inhibitory receptor
AUTHOR: Burshtyn, D.N.; Scharenberg, A.M.; Wagtmann, N.; Rajagopalan, S.; Berrada, K.; Yi, Taolin; Kinet, J.-P.; Long, E.O.
CORPORATE SOURCE: Lab. Immunogenetics, Natl. Inst. Allergy and Infect. Dis., Natl. Inst. Health, 12441 Parklawn Dr., Rockville, MD 20852, USA
SOURCE: IMMUNITY, (**1996**) vol. 4, no. 1, pp. 77-85. ISSN: 1074-7613.
DOCUMENT TYPE: Journal
FILE SEGMENT: F
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cytolysis of target cells by natural killer (**NK**) **cells** and by some cytotoxic T cells occurs unless prevented by inhibitory receptors that recognize MHC class I on target cells. Human **NK cells** express a p58 inhibitory receptor specific for HLA-C. We report association of the tyrosine phosphatase HCP with the p58 receptor in **NK cells**. HCP association was dependent on tyrosine phosphorylation of p58. Phosphotyrosyl peptides corresponding to the p58 tail bound and **activated** HCP in vitro. Furthermore, introduction of an inactive mutant HCP into an **NK cell** line prevented the p58-mediated inhibition of target cell lysis. These data imply that the inhibitory function of p58 is dependent on its tyrosine phosphorylation and on recruitment and **activation** of HCP.

L6 ANSWER 13 OF 24 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 95347399 MEDLINE
DOCUMENT NUMBER: 95347399 PubMed ID: 7621874
TITLE: Early appearance of T cell receptor alpha beta + CD4- CD8- T cells with a skewed variable region repertoire after infection with Listeria monocytogenes.
AUTHOR: Matsuzaki G; Li X Y; Kadena T; Song F; Hiromatsu K; Yoshida H; Nomoto K
CORPORATE SOURCE: Department of Immunology, Kyushu University, Fukuoka, Japan.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (**1995 Jul**) 25 (7)

1985-91.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950911
Last Updated on STN: 19950911
Entered Medline: 19950829

AB We found that the number of T cell receptor (TCR) alpha beta + CD4- CD8- T cells increased in the peritoneal cavity on day 5 after an intraperitoneal infection with Listeria monocytogenes strain EGD together with TCR gamma delta + CD4- CD8- T cells. Thereafter, the TCR alpha beta + CD4- CD8- T cells decreased to a normal level by day 14. The TCR alpha beta + CD4- CD8- T cells showed an **activated** T cell phenotype (L-selectin CD44 +) and expressed CD45/B220 and interleukin-2 receptor beta, but did not express heat stable antigen, which is expressed by the immature CD4- CD8- thymocytes. Furthermore, 20-30% of the TCR alpha beta + CD4- CD8- T cells expressed the NK1.1 **natural killer cell** marker. Analysis of the TCR V region repertoire of the TCR alpha beta + CD4- CD8- T cells induced by L. monocytogenes infection showed that more than 80% of the TCR alpha beta + CD4- CD8- T cells expressed TCR V beta 8 detected by anti-TCR V beta 8.1 and 8.2 mAb, and a reverse transcription-polymerase chain reaction analysis of V alpha 14 relative to V alpha 11 expression revealed that the TCR alpha beta + CD4- CD8- T cells expressed a higher level of V alpha 14, which was reported to be preferentially expressed by TCR alpha beta + CD4- CD8- thymocytes rather than conventional CD4+ T cells. The TCR alpha beta + CD4- CD8-T cells showed a proliferative response to anti-TCR alpha beta mAb stimulation. In contrast, they showed no response to stimulation with either Listeria antigen or 65-kDa **heat shock protein** of Mycobacterium bovis, which do stimulate the Listeria-specific TCR alpha beta + CD4- CD8- T cells and the Listeria-induced TCR gamma delta + T cells, respectively. These results suggest that the TCR alpha beta + CD4- CD8- T cells may recognize a restricted set of self antigens induced by L. monocytogenes infection, and that they contribute to host protection at an early stage of infection.

L6 ANSWER 14 OF 24 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 96091802 MEDLINE
DOCUMENT NUMBER: 96091802 PubMed ID: 7495755
TITLE: Intra-epithelial lymphocytes. Evidence for regional specialization and extrathymic T cell maturation in the human gut epithelium.
AUTHOR: Lundqvist C; Baranov V; Hammarstrom S; Athlin L; Hammarstrom M L
CORPORATE SOURCE: Department of Immunology, Umea University, Sweden.
SOURCE: INTERNATIONAL IMMUNOLOGY, **(1995 Sep)** 7 (9) 1473-87.
Journal code: 8916182. ISSN: 0953-8178.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 19960217
Last Updated on STN: 19960217
Entered Medline: 19960118

AB The human gut epithelium is a unique immunological compartment, containing substantial amounts of intra-epithelial lymphocytes (IEL) with unknown functions. In this study we show that distinct and unusual subpopulations of IEL are present at different levels of human intestine. IEL phenotypes in normal jejunum, ileum and colon were compared using immunoflow cytometry and immunohistochemistry. The expression of mRNA for

recombination-**activating** gene-1 (RAG-1) in IEL from all three levels was compared using reverse-transcription polymerase chain reaction, and the morphology of IEL in situ was determined using immunoelectron microscopy. Surface marker profiles of isolated intestinal epithelial cells at all three levels were also investigated. On average the proportion of TCR gamma delta IEL was comparable in jejunum than ileum and colon and varied in phenotype with gut level. CD4-CD8-TCR alpha beta IEL dominated in colon but were absent in jejunum. CD8+ TCR alpha beta IEL were present at all levels but only in jejunum did they constitute the majority of all IEL. CD4+ TCR alpha beta IEL were present in similar frequencies at all levels of the gut. In general, the majority of IEL had an **activated** phenotype (CD45RO+, alpha E beta 7+). Furthermore, IEL exhibited phenotypes which are rare in peripheral blood. The thymocyte markers CD1a and CD1c as well as the **NK cell** marker CD56 were expressed on a fraction of TCR alpha beta and TCR gamma delta IEL. A small population of 'null' cells (CD45+ TCR/CD#-CD20-CD14-CD15- cells) was also present at equal proportions along the gut. Jejunal but not colonic IEL expressed RAG-1 mRNA suggesting that extrathymic T cell maturation occurs in the epithelium of small intestine. RAG-1 was expressed in CD2+TCR/CD3- and CD3+/TCR-IEL. Ultrastructurally, IEL often formed small clusters and intimate contacts with epithelial cells, suggesting cell cooperation within the epithelium. Some IEL had pseudopodium-like extensions penetrating the epithelial basement membrane suggesting transmigration. Epithelial cells in small intestine but not colon expressed **heat shock protein** 60 and HLA-DR. CD1a, CD1b and CD1c were not expressed on intestinal epithelial cells at any level. The distinct surface marker profiles of IEL and epithelial cells along small and large intestine suggest functional regional specialization and are compatible with the hypothesis that TCR alpha beta IEL participate in immune reactions to lumenal antigens while TCR gamma delta IEL perform surveillance of the epithelium.

L6 ANSWER 15 OF 24 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 96028031 MEDLINE
DOCUMENT NUMBER: 96028031 PubMed ID: 7546642
TITLE: Some new aspects of molecular mechanisms of cyclosporin A effect on immune response.
AUTHOR: Zav'yalov V P; Denesyuk A I; Lundell J; Korpela T
CORPORATE SOURCE: Institute of Immunology, Lyubuchany, Moscow Region, Russia.
SOURCE: APMIS, **(1995 Jun)** 103 (6) 401-15. Ref: 121
Journal code: 8803400. ISSN: 0903-4641.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19980206
Entered Medline: 19951114

AB A few protein targets were found to display a specific high-affinity interaction with the immunosuppressant cyclosporin A (CsA): cytosolic cyclophilins (CyP)A, B, C, D, E containing from 122 to 174 amino acid residues in a polypeptide chain, and secreted forms of CyP; CyP-40, 40-kDa CsA-binding polypeptide complexed with steroid receptor (SR); CyP-related 150-kDa receptor of natural killer (**NK**) **cells**; interleukin 8 (IL-8); actin; a family of molecular chaperones **hsp70** and P-glycoprotein (P-GP). All CyPs possess peptidyl-prolyl cis-trans isomerase activity (PPIase) and may serve as ATP-independent molecular chaperone proteins. The CsA-CyP complexes are specific inhibitors of Ca(2+)-and calmodulin-dependent protein phosphatase calcineurin (CaN). The inhibition of CaN blocks the **activation** of genes of IL-2, IL-2R, IL-4, etc. in T cells. In addition, immunosuppressive and/or antiinflammatory activity of CsA can be executed

via CyP-40 and **hsp** 70 complexed with SR, and following the interaction with CyP-related receptor of NK and with IL-8. CsA binding to CyPC, P-GP and actin may throw light on the biochemical events leading to nephrotoxicity and graft vessel disease, two major side effects produced by CsA. The discovery of the interaction of human immunodeficiency virus type 1 (HIV-1) Gag protein with CyP and effective disruption of this interaction by CsA may be important for our understanding of the pathology caused by this immunosuppressive virus and will inspire therapeutic strategies to nip HIV in the bud. Bacterial immunophilins (ImPs) contribute to the virulence of pathogenic microorganisms. Elucidation of molecular mechanisms of microbial ImPs' action in the pathogenesis of bacterial infections may lead to new strategies for designing antibacterial drugs.

L6 ANSWER 16 OF 24 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 94165499 MEDLINE
DOCUMENT NUMBER: 94165499 PubMed ID: 7509833
TITLE: Immunomorphologic studies of human decidua-associated lymphoid cells in normal early pregnancy.
AUTHOR: Mincheva-Nilsson L; Baranov V; Yeung M M; Hammarstrom S; Hammarstrom M L
CORPORATE SOURCE: Department of Immunology, University of Umea, Sweden.
SOURCE: JOURNAL OF IMMUNOLOGY, **(1994 Feb 15)** 152 (4) 2020-32.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940412
Last Updated on STN: 19960129
Entered Medline: 19940407

AB Human decidual lymphocytes from early, normal pregnancy were characterized in situ with respect to ultrastructure and distribution of subsets. The ultrastructure of isolated decidual gamma delta T cells was also studied. CD45+ cells comprised 11 +/- 2% of all decidual cells. The majority were localized in large lymphoid cell clusters (LCC), near endometrial glands, or as intraepithelial lymphocytes (IEL) in glandular epithelium. The major cell populations in LCC were CD56+TCR-gamma delta+ cells, CD56+ cells, TCR-alpha beta+CD4+ cells, and TCR-alpha beta+CD8+ cells. All expressed **activation** markers (CD45RO, Kp43, and/or HML-1) and MHC class II Ag (HLA-DR, HLA-DP, and/or HLA-DQ). No B cells were found. Almost all IEL were **activated** TCR-gamma delta+ cells (CD56+ and CD56-). The glandular epithelial cells expressed **heat shock protein** 60 at the basolateral side facing the TCR-gamma delta+ IEL. Decidual lymphocytes displayed cytoplasmic processes, microvilli, characteristic cytoplasmic granules, and had intimate contact with neighboring cells. Lymphocytes in the outer rim of LCC and the stroma showed signs of cellular movement. Two main morphotypes of gamma delta T cells could be distinguished. One had single microvilli, membrane-bound granules, and nuclear inclusions. The other had many microvilli, nonmembrane-bound granules and cytoplasmic multivesicular bodies. Our data suggest that LCC are centers of immune reactivity where T and **NK cells** become **activated**. The **activated** cells may guard against infections and undue trophoblast invasion and/or be involved in modulating the local maternal immune system toward unresponsiveness against the semiallogeneic fetus.

L6 ANSWER 17 OF 24 CANCERLIT
ACCESSION NUMBER: 95607573 CANCERLIT
DOCUMENT NUMBER: 95607573
TITLE: Induction of non-mhc restricted killer cells: differential induction of effector populations by tumour cell lines.
AUTHOR: Selin L K

CORPORATE SOURCE: Univ. of Manitoba, Canada.
SOURCE: Diss Abstr Int [B], **(1994)** 55 (3) 814.
ISSN: 0419-4217.
DOCUMENT TYPE: (THESIS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950608
Last Updated on STN: 19970509

AB The nonadaptive immune response characterized by non-MHC-restricted cytotoxic effectors appears to play a significant role in host cellular immunity against both infectious diseases and tumors. It is possible that cytotoxic responsiveness of these effectors to 'altered' tumor cells also implies a capacity to induce the effector population. A systematic examination of different tumor cell lines did demonstrate a differential ability of tumor cell lines to induce effectors both **NK cells** and gamma,delta T cells. The properties and characteristics which made tumor cell lines into effective inducers were examined as well as the nature of the effector populations. Lymphoblastoid B cell lines (LBL) were the most effective inducers of non-MHC restricted killer cell activity as they induced enhanced levels of cytotoxic activity and stimulated proliferative responses in the responder population. Different LBL alone or in conjunction with IL-2 were able to stimulate non-MHC restricted cytotoxic activity in **NK cells**, gamma,delta and alpha,beta T cells. The phenotype(s) which was induced was dependent on the specific LBL used in the induction system as well as the presence of IL-2. The presence of Epstein-Barr virus (EBV) infection was found to significantly enhance LBL cytotoxic and proliferation inductive capacity as well as the proportion of CD16+ cells. Studies using EBV+ and EBV- LBL suggested that at least two parameters were involved in the EBV+ LBL induction process, the presence of a stimulating antigen on the LBL which specifically stimulates CD16+ cells and a second element which results in the induction of IL-2. Neither parameter was sufficient alone. Consistent with the hypothesis that a LBL cell surface molecule was involved in the induction was the observations that cellular contact was found to be essential. As well antibodies to 3 classes of adhesion molecules (CD2, CD18, and CD29) were found to inhibit LBL induction of non-MHC restricted killer cell activity. Two LBL, RPMI 8226 and Daudi were found to be potent inducers of Vgamma9 expressing T cells. This inductive capacity was not a general property of LBL nor did it relate to the presence of EBV nor to the tumor type of the B cell line. RPMI 8226 induced a population of gamma,delta T cells which were heterogeneous in terms of their cell surface markers, patterns of proliferation and cytotoxic responses. A member of the groEL **HSP** family (**HSP** 58) has been suggested as the inducing molecule in Daudi cells. Although anti-**HSP** 58 was inhibitory to gamma,delta T cell induction by RPMI 8226, Daudi and mycobacterial products evidence is presented which suggests this may not be a specific effect. Collectively, the results suggest that some LBL cell surface stimulus can induce an **activation** and expansion of non-MHC restricted killer cells. In the present studies the expansion of CD16+ and gamma,delta TCR+ effectors were examined. This inductive ability of LBL appears to relate in part to viral infection and in part to the phenotypic properties of the inducer. The nature of the stimulus is still unclear at this time but these results do suggest that there is a clear distinction between target susceptibility and inductive capacity. (Abstract shortened by UMI.) (Full text available from University Microfilms International, Ann Arbor, MI, as Order No. AADNN-85917)

L6 ANSWER 18 OF 24 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 94044776 MEDLINE
DOCUMENT NUMBER: 94044776 PubMed ID: 8228242
TITLE: 70 kDa heat shock cognate protein is a transformation-associated antigen and a possible target for the host's anti-tumor immunity.

AUTHOR: Tamura Y; Tsuboi N; Sato N; Kikuchi K
CORPORATE SOURCE: Department of Pathology, Sapporo Medical University School of Medicine, Japan.
SOURCE: JOURNAL OF IMMUNOLOGY, **(1993 Nov 15)** 151 (10) 5516-24.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19990129
Entered Medline: 19931210

AB We previously investigated a novel heat-inducible transformation-associated cell surface Ag that is expressed on the **activated** H-ras oncogene-transformed rat fibrosarcoma W31, but not its parental nontransformed fibroblast WFB. This Ag was detected by mAb 067. Herein, we characterized the molecular nature of the Ag by using anti-**heat shock protein** (**HSP**) mAb. The accumulated data indicated that the cell surface expression of Ag was clearly enhanced by several stressors, such as TNF, L-azetidine-2-carboxylic acid, and sodium arsenite. The immunoprecipitate made with mAb 067 and W31 cell lysates reacted with anti-rat 70 kDa heat shock cognate (HSC) mAb, TG5E, indicating that 067-defined Ag may be a rat 70 kDa HSC. Because this Ag seemed to be one of the transformation-associated Ag of WFB, we further studied whether it could play an important role in the host's anti-tumor immunity. Peripheral T cells of rats primed with live BCG showed cytotoxicity to W31 but not to WFB. Because the possibility existed that **HSP** may interact with certain populations of T cells, we focused on the reactivity of CD4-CD8- double negative T (DNT) cells against 067-defined molecule. DNT cells from spleen and PBL of live BCG-primed rats showed the cytotoxicity against W31 cells. This cytotoxicity was completely blocked by mAb 067 and anti-CD3 mAb. However, it was not blocked by mAb R48B1 and 109, which detect the MHC class I nonpolymorphic determinant and a target molecule of the cytolysis by poly I:C-induced **NK cells**, respectively. Furthermore, brefeldin A was able to block the cytotoxicity against W31 targets by DNT cells, but not by **NK cells**. These data suggest that 70 kDa HSC may be a tumor Ag and may act as a presenting molecule perhaps complexed with cellular peptides to certain DNT cells.

L6 ANSWER 19 OF 24 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 94169339 MEDLINE
DOCUMENT NUMBER: 94169339 PubMed ID: 8123821
TITLE: [The interaction of human natural killers with target cells of the K562 line and its sublines characterized by multiple drug resistance and thermoresistance].
Vzaimodeistvie estestvennykh killerov cheloveka s kletkami-misheniami linii K562 i ee subliniiami, kharakterizuiushchimisia mnozhestvennoi lekarstvennoi ustoichivost'iu i teploustoichivost'iu.
AUTHOR: Davtian T K; Blinova G I; Ignatova T N; Aleksanian Iu T; Meliksetian M B
SOURCE: BIULLETEN EKSPERIMENTALNOI BIOLOGII I MEDITSINY, **(1993 Dec)** 116 (12) 616-8.
Journal code: 0370627. ISSN: 0365-9615.
PUB. COUNTRY: RUSSIA: Russian Federation
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940420
Last Updated on STN: 19970203
Entered Medline: 19940413

AB Target cells, K562 strain and its sublines characterized by multiple drug resistance (MDR) do not differ in their susceptibility to human **natural killer cells** (NK) but MDR cells are more susceptible to cytotoxic action of lymphokine-**activated** cells (LAC) and to **NK cells** in the presence of a selective agent adriamycin. Target cells death is characterized by fragmentation of nuclear DNA. It has been established that K562 thermotolerant subclone is more resistant to NK and LAC than other clones. **Heat shock protein** synthesis may have a protective impact in target cells death during interaction with NK and LAC cells.

L6 ANSWER 20 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:480711 BIOSIS
DOCUMENT NUMBER: PREV199396114311
TITLE: Specific **activation** of human peripheral blood gamma/delta positive T lymphocytes by sonicated antigens of Mycobacterium tuberculosis: Role in vitro in killing human bladder carcinoma cell lines.
AUTHOR(S): Wang, M.-H.; Chen, Y.-Q.; Gercken, J.; Ernst, M.; Boehle, A.; Flad, H.-D.; Ulmer, Artur J. (1)
CORPORATE SOURCE: (1) Div. Cellular Immunol., Dep. Immunol. Cell Biol., Forschungsinstitut Borstel, Parkallee 22, D-23845 Borstel Germany
SOURCE: Scandinavian Journal of Immunology, (1993) Vol. 38, No. 3, pp. 239-246.
ISSN: 0300-9475.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Tumour regression induced in cancer patients by local instillation of Bacillus Calmette-Guerin (BCG) into the bladder has been considered to be mainly mediated by **activated** cellular immunity and inflammatory reactions. In the present study we investigated the cytotoxicity of T cells bearing gamma/delta T-cell receptors (gamma/delta+ T cells) against bladder carcinoma cells in vitro. Long-term cultured gamma/delta+ T-cell lines from peripheral blood lymphocytes of healthy donors were established by stimulation with sonicated cell wall-associated antigens of Mycobacterium tuberculosis (SMA). These gamma/delta+ T cells lack the natural killer (NK) markers CD16 and CD56, as determined by flow cytometry. The SMA-specific gamma/delta+ T cells exhibited profound cytotoxicity against two NK-resistant bladder tumour cell lines as well as against NK-sensitive tumour cells in a non-major histocompatibility complex-restricted manner. The pattern of tumour cells killed by gamma/delta+ T cells differed significantly from those of **NK cells** and lymphokine-**activated** killer LAK cells. Furthermore, we tested the effects of recombinant human cytokines, including interleukin (IL)-1, IL-2, IL-4, IL-6, interferon (IFN)-gamma and tumour necrosis factor (TNF), on gamma/delta+ T-cell-mediated cytotoxicity. It was shown that the addition of recombinant TNF in co-incubation could augment gamma/delta+ T-cell-mediated killing of two bladder tumour cell lines, but not of cells of the erythroleukaemia cell line K562. Based on these results it was concluded that mycobacterial antigens could specifically **activate** resting gamma/delta+ T cells. The cytotoxicity of gamma/delta+ T cells against bladder tumour cells and its selective enhancement by TNF may be an important mechanism involved in bladder tumour regression induced by intravesical instillation of BCG.

L6 ANSWER 21 OF 24 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 93352110 MEDLINE
DOCUMENT NUMBER: 93352110 PubMed ID: 8349312
TITLE: Changes in the level of perforin and its transcript during effector and target cell interactions.
AUTHOR: Kim K K; Blakely A; Zhou Z; Davis J; Clark W; Kwon B S
CORPORATE SOURCE: Department of Microbiology and Immunology, Indiana

University School of Medicine, Indianapolis 46202.
CONTRACT NUMBER: DE10525 (NIDCR)
K11DE00310 (NIDCR)
MAI-28175 (NIAID)
SOURCE: IMMUNOLOGY LETTERS, **(1993 May)** 36 (2) 161-9.
Journal code: 7910006. ISSN: 0165-2478.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199309
ENTRY DATE: Entered STN: 19931001
Last Updated on STN: 20000303
Entered Medline: 19930915

AB Perforin is a cytoplasmic granule protein expressed in cytotoxic lymphocytes, and is capable of lysing target cells. This protein is induced as cytotoxic T cells are **activated**, and the mRNA expression is modulated by various stimulators. These observations suggest possible changes in the level of perforin transcripts and protein when killer lymphocytes meet specific target cells leading to target cell death. To address this question, we examined three murine T-cell clones and primary human **NK cells** in perforin expression. When the cytotoxic lymphocytes were exposed to sensitive targets, perforin mRNA disappeared within 5 to 30 min and appeared within an hour thereafter. Among the murine T cell clones, L3 and OE4 showed two phases of mRNA decrease while human **NK cells** and the third murine T cell clone, AB.1, showed only one phase of mRNA loss during a 240 min period. The data indicate that when cytotoxic lymphocytes receive signals from a sensitive target, the cells rapidly degrade previously accumulated perforin mRNA and synthesize new transcripts. Interestingly, **heat shock protein** 70 mRNA was induced as the perforin mRNA levels recovered, while P55 Il-2 receptor mRNA was downregulated within 5 min after exposure to targets. The perforin protein level also rapidly decreased immediately after the interaction with the target, followed by a recovery, and then another decrease as seen in primary human **NK cells**, OE4 and L3 cells. However, in the AB.1 clone, no change in perforin content was detectable, despite the loss of perforin mRNA.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 22 OF 24 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 91318159 MEDLINE
DOCUMENT NUMBER: 91318159 PubMed ID: 1861074
TITLE: **Natural killer cell** clones can efficiently process and present protein antigens.
AUTHOR: Roncarolo M G; Bigler M; Haanen J B; Yssel H; Bacchetta R; de Vries J E; Spits H
CORPORATE SOURCE: DNAX Research Institute, Human Immunology Department, Palo Alto, CA 94304-1104.
SOURCE: JOURNAL OF IMMUNOLOGY, **(1991 Aug 1)** 147 (3) 781-7.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910922
Last Updated on STN: 19910922
Entered Medline: 19910830

AB **NK cell** clones obtained from three different donors were tested for their ability to present soluble proteins to Ag-specific T cell clones. All NK clones were CD2+CD3-CD56+, whereas the expression of CD16 varied from clone to clone. The **NK cell** clones were able to process and present tetanus toxoid (TT) to TT-specific T cell clones in a class II HLA restricted manner. The capacity of **NK**

cell clones to function as APC was also observed using the house dust mite allergen Der p I and the Der p I-derived peptide Val89-Cys117. As with EBV-transformed B cell line, **NK cell** clones could present the peptide 3-13 derived from the 65-kDa **heat shock protein** of Mycobacterium leprae, but they were unable to present the whole M. leprae Ag. Freshly isolated **NK cells**, IL-2-**activated NK cells**, and **NK cell** lines expanded in vitro could also process and present TT. The ability of the different NK populations to act as accessory cells correlated with their levels of class II HLA expression. These data demonstrate that **NK cell** clones can efficiently function as APC, however they may be restricted in the types of Ag that they can process.

L6 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:104251 CAPLUS
DOCUMENT NUMBER: 116:104251
TITLE: Rapid loss of perforin and serine protease RNA in cytotoxic lymphocytes exposed to sensitive targets
AUTHOR(S): Bajpai, A.; Kwon, B. S.; Brahmi, Z.
CORPORATE SOURCE: Sch. Med., Indiana Univ., Indianapolis, IN, 46202-5128, USA
SOURCE: Immunology (**1991**), 74(2), 258-63
CODEN: IMMUAM; ISSN: 0019-2805
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It was previously reported that cytotoxic lymphocytes, when exposed to sensitive target cells, temporarily lose their lytic potential. The mechanism leading to this loss of lytic activity is still unknown but it is reversible and the lytic potency can be recovered when the effector cells are incubated with interleukin-2 (IL-2) for 12-14 h. In this study, the authors have investigated the regulation of RNA coding for perforin and for two serine proteases, **HSP1** and **HSP2**, in cytotoxic lymphocytes exposed to sensitive targets. Perforin and the two serine proteases are contained in granules of major histocompatibility complex (MHC)-restricted and non-MHC-restricted cytotoxic lymphocytes, but their exact role in the lytic mechanism is still debated. Here four different human cytotoxic lymphocytes (CTL) were used as effector cells: an MHC-restricted CTL (SG-CTL), a non-MHC-restricted CTL (IE6), a natural killer (NK)-like cell line (3.3) and lymphokine-**activated** killer (LAK) cells. In all effector cells there was a rapid loss of perforin and of serine protease RNAs within 5 min following the addn. of sensitive targets. The effector cells recovered the RNA messages as early as 30 min, although the kinetics of recovery was faster with CTL than with NK-like or LAK effector cells. When the effector cells were exposed to resistant targets no loss of perforin or serine protease RNAs could be detected. Incubation of the effector cells with cycloheximide, prior to the addn. of sensitive targets, did not block message loss, indicating that de novo protein synthesis was not required in this process. Cycloheximide treatment, however, inhibited the recovery of perforin and serine protease RNAs. These results indicate that the target-mediated loss of lytic activity in cytotoxic lymphocytes may be a consequence of the down-regulation of perforin or of serine protease transcripts, or both.

L6 ANSWER 24 OF 24 CANCERLIT
ACCESSION NUMBER: 90665511 CANCERLIT
DOCUMENT NUMBER: 90665511
TITLE: CELLULAR IMMUNITY AND THE IMMUNOTHERAPY OF CANCER.
AUTHOR: Anonymous
CORPORATE SOURCE: No affiliation given.
SOURCE: J Cell Biochem, **(1990)** (Suppl 14B) 49-111.
ISSN: 0730-2312.
DOCUMENT TYPE: Book; (MONOGRAPH)
LANGUAGE: English

FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199009
ENTRY DATE: Entered STN: 19941107
Last Updated on STN: 19970509

AB Abstracts are presented from the plenary and poster sessions of the symposium on cellular immunity and the immunotherapy of cancer, held January 27 to February 3, 1990, in Park City, UT, as part of the 19th Annual UCLA Symposia on Molecular and Cellular Biology. Discussions covered T-cell recognition of antigen and the T-cell receptor, effector cell **activation** and target cell binding, animal models of adoptive therapy, idiotypes and T-cell recognition of tumor antigens, human tumor-specific T-cell lines and clones, T-cell growth factors, allograft rejection and autoimmunity, clinical trials of adoptive immunotherapy, T-cell **activation** and antigen recognition, cell trafficking and endothelial interactions, nonspecific immunity, and clinical and preclinical studies of T-cell-mediated rejection. Specific topics included T-cell-defined transplantation antigens expressed by tumor cells, antigen processing and presentation by melanoma cells, **activation** of **natural killer cells**, T-cell 'adhesion' molecules, UV radiation and immunity to murine melanomas, graft rejection in tumor-bearing animals, anti-idiotypes in cancer patients, human tumor antigens, cellular immunity in sarcomas, T-cell therapy in retroviral leukemia, interleukin-6 in host-tumor interactions, **heat-shock proteins** in autoimmune disease, immunotherapy of human melanomas, beta 1-integrin receptors on melanoma clones, tumor necrosis factor-alpha and interferon-gamma secretion in lymphokine-**activated** killer cells, T-cell-mediated tumor cytolysis, T-cell antigen receptor gene regulation, steady-state protein synthesis in human neuroblastoma cells, retrovirus-mediated transfer of human interleukin-2 (IL-2) into mouse hematopoietic stem cells, epidermal growth factor receptors, tumor-infiltrating lymphocytes in uveal melanoma, antibody-directed lymphocytes, tumor-infiltrating T cells in human gliomas, rejection of sarcoma cells following transfection of MHC class II genes, cell surface proteins of murine tumors, eradication of adenovirus E1-induced tumors, and role of IL-2-**activated** killer cells in rejection of allografts.

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=>
=> d history

     (FILE 'HOME' ENTERED AT 17:11:13 ON 15 DEC 2002)

    · FILE 'MEDLINE, BIOSIS, CANCERLIT, LIFESCI, BIOTECHDS, CAPLUS' ENTERED AT
     17:11:29 ON 15 DEC 2002
L1         74620 S HSP## OR (HEAT(W)SHOCK(W)(PROTEIN# OR PEPTIDE#))
L2         83305 S (NK OR (NATURAL(W)KILLER))(W)CELL#
L3           298 S L1 AND L2
L4            92 S L3 AND ACTIVAT?
L5            57 S L4 AND PY<2000
L6            24 DUP REM L5 (33 DUPLICATES REMOVED)

=> s hsp7# or (heat(w)shock(w)protein(w)7#)
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L7        26787 HSP7# OR (HEAT(W) SHOCK(W) PROTEIN(W) 7#)

=> s l7 and l2
L8          128 L7 AND L2

=> s l8 and py<2000
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   4 FILES SEARCHED...
L9           68 L8 AND PY<2000
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=> s l9 not l5
L10          50 L9 NOT L5

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11          20 DUP REM L10 (30 DUPLICATES REMOVED)

=> d ibib abs tot

L11  ANSWER 1 OF 20     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   2000023566     MEDLINE
DOCUMENT NUMBER:    20023566   PubMed ID: 10560910
TITLE:              Heat shock protein 70
                    (Hsp70) stimulates proliferation and cytolytic
                    activity of natural killer
                    cells.
AUTHOR:             Multhoff G; Mizzen L; Winchester C C; Milner C M; Wenk S;
                    Eissner G; Kampinga H H; Laumbacher B; Johnson J
CORPORATE SOURCE:   Department of Hematology/Internistic Oncology, University
                    Hospital Regensburg, Germany.. gabriele.multhoff@klinik.uni-
                    regensburg.de
SOURCE:             EXPERIMENTAL HEMATOLOGY, (1999 Nov) 27 (11)
                    1627-36.
                    Journal code: 0402313. ISSN: 0301-472X.
PUB. COUNTRY:       Netherlands
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        199911
ENTRY DATE:         Entered STN: 20000111
                    Last Updated on STN: 20000111
                    Entered Medline: 19991124
AB   We previously demonstrated that lysis of tumor cells that express
     Hsp70, the highly stress-inducible member of the HSP70
     family, on their plasma membrane is mediated by natural killer (NK
     ) cells. Here, we studied the effects of different proteins of
     the HSP70 family in combination with interleukin 2 (IL-2) on the
     proliferation and cytotoxic activity of human NK cells
     in vitro. Proliferation of NK cells was significantly
     enhanced by human recombinant Hsp70 (rHsp70) and to a lesser
     extent by rHsp70homC, the recombinant C-terminal peptide-binding domain
     derived from Hsp70hom, but not by the constitutive Hsc70 or DnaK, the
     Escherichia coli analogue of human Hsp70. Even rHsp70 protein
     alone moderately enhances proliferation and cytolytic activity of
     NK cells, thus indicating that the stimulatory effect is
     not strictly dependent on IL-2. NK cells stimulated
     with rHsp70 protein also exhibit an increased secretion of interferon
     gamma (IFN-gamma). The phenotypic characterization of NK
     cells with specificity for Hsp70-expressing tumor cells
     revealed a CD16dim/CD56bright and increased CD57 and CD94 expression. The
     cytolytic activity of NK cells also was significantly
     reduced when a CD94-specific antibody or rHsp70 was added directly before
     the cytotoxicity assay, whereas other antibodies directed against CD57 and
     major histocompatibility complex class I molecules or Hsp70
     proteins, including Hsc70 and DnaK, did not affect the NK-mediated
     killing. However, long-term incubation of NK cells
     with rHsp70 protein enhances not only the proliferative but also the
     cytolytic response against Hsp70-expressing tumor cells. Our
     results indicate that the C-terminal domain of Hsp70 protein
     affects not only the proliferative but also the cytolytic activity of a
     phenotypically distinct NK cell population with
     specificity for Hsp70-expressing tumor cells. 1999 International
     Society for Experimental Hematology.

L11  ANSWER 2 OF 20     MEDLINE                          DUPLICATE 2
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ACCESSION NUMBER: 1999189779 MEDLINE
DOCUMENT NUMBER: 99189779 PubMed ID: 10089909
TITLE: Synergistic effects of heat and ET-18-OCH3 on membrane expression of **hsp70** and lysis of leukemic K562 cells.
AUTHOR: Botzler C; Ellwart J; Gunther W; Eissner G; Multhoff G
CORPORATE SOURCE: GSF-Institute of Molecular Immunology, Munich, Germany.
SOURCE: EXPERIMENTAL HEMATOLOGY, **(1999 Mar)** 27 (3) 470-8.
Journal code: 0402313. ISSN: 0301-472X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990504
Last Updated on STN: 19990504
Entered Medline: 19990421

AB We previously reported that cell surface expression of **hsp70**, the major stress inducible member of the 70-kDa heat shock protein family, is inducible by nonlethal heat as well as by treatment with the membrane-interactive compound alkyl-lysophospholipid 1-octadecyl-2-methyl-rac-glycero-3-phosphocholine (ET-18-OCH3) selectively on human tumor cell lines. Plasma membrane expression of **hsp70** increases selectively the sensitivity of tumor cells to lysis and, therefore, might play an important role in the antitumor immune response. Here, we demonstrate that a combined treatment consisting of sublethal heat (41.8 degrees C) and a noncytotoxic concentration of ET-18-OCH3 (25 micrograms/mL) results in a synergistic increase in the amount of cell membrane-bound **hsp70** on leukemic K562 cells and on freshly isolated bone marrow of a chronic myelogeneous leukemia (CML) patient, but not on peripheral blood lymphocytes or CD34+ hematopoietic progenitor cells of healthy human individuals. Under these conditions the repopulating capacity of progenitor cells was not influenced. The increased **hsp70** membrane expression on leukemic K562 cells results in a significantly increased sensitivity to lysis mediated by **natural killer cells**. In contrast to leukemic cells, the lysis of peripheral blood lymphocytes and CD34+ progenitor cells that lack expression of **hsp70** on their plasma membrane was not negatively influenced by this treatment. A nonspecific disruption of the plasma membrane could be excluded, because treatment with a nontoxic concentration of the detergent Tween20 did not have an influence on **hsp70** cell surface expression or on the sensitivity to lysis. Our findings might have further clinical implications with respect to purging of bone marrow from patients suffering from leukemia at sublethal conditions to induce a tumor-selective immune response.

L11 ANSWER 3 OF 20 MEDLINE
ACCESSION NUMBER: 1999246045 MEDLINE
DOCUMENT NUMBER: 99246045 PubMed ID: 10231014
TITLE: Heat shock protein-based therapeutic strategies against human immunodeficiency virus type 1 infection.
AUTHOR: Brenner B G; Wainberg M A
CORPORATE SOURCE: McGill AIDS Centre, Lady Davis Institute, Jewish General Hospital, and Department of Experimental Surgery, McGill University, Montreal, Quebec, Canada..
mdbl@musica.mcgill.ca
SOURCE: INFECTIOUS DISEASES IN OBSTETRICS AND GYNECOLOGY, **(1999)** 7 (1-2) 80-90. Ref: 82
Journal code: 9318481. ISSN: 1064-7449.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS

ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990730
Last Updated on STN: 19990730
Entered Medline: 19990721

AB Heat shock proteins (hsps) and cyclophilins (CypA) are intracellular chaperone molecules that facilitate protein folding and assembly. These proteins are selectively expressed in cells following exposure to a range of stress stimuli, including viral infection. Hsp species are highly immunogenic, eliciting humoral, cytotoxic T lymphocyte (CTL), and natural killer (**NK**) **cell** responses against viruses, tumours, and infectious diseases. This review discusses the roles of stress proteins in immunity and viral life cycles, vis-a-vis the development of Hsp-based therapeutic strategies against human immunodeficiency virus type-1 (HIV-1) infection. Cumulative findings are cited implicating the requirement of CypA in HIV-1 replication and formation of infectious virions. Studies by our group show the upregulated expression of hsp27 and **hsp70** during single-cycle HIV infections. These species redistribute to the cell surface following HIV-infection and heat stress, serving as targets for NK and antibody-dependent cellular cytotoxicity. Co-immunoprecipitation and Western blot studies show that hsp27, **hsp70**, and **hsp78** complex with HIV-1 viral proteins intracellularly. **Hsp70**, hsp56, and CypA are assembled into HIV-1 virions. The ability of hsps to interact with HIV-1 viral proteins, combined with their inherent adjuvant and immunogenic properties, indicates that hsps may serve as vehicles for antigen delivery and the design of vaccines against acquired immunodeficiency syndrome.

L11 ANSWER 4 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:261889 BIOSIS
DOCUMENT NUMBER: PREV199900261889
TITLE: Meeting report on the International Congress on Hyperthermia in Clinical Oncology, Venice 1998.
AUTHOR(S): Multhoff, Gabriela (1); Falk, Martin
CORPORATE SOURCE: (1) GSF-Institute of Molecular Immunology, Marchioninistr. 25, 81377, Munich Germany
SOURCE: Cell Stress & Chaperones, (**March, 1999**) Vol. 4, No. 1, pp. 54-59.
ISSN: 1355-8145.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 5 OF 20 BIOTECHDS COPYRIGHT 2002 THOMSON DERWENT AND ISI
ACCESSION NUMBER: 1998-07085 BIOTECHDS
TITLE: Human colonic carcinoma cells with stable, high or low level, expression of **heat shock protein -72**;
colon carcinoma cell culture and cancer therapy
AUTHOR: Multhoff G
PATENT ASSIGNEE: GSF-Res.Inst.Environ.Health
LOCATION: Oberschleissheim, Germany.
PATENT INFO: EP 843005 **20 May 1998**
PRIORITY INFO: DE 1996-1064742 15 Nov 1996
DOCUMENT TYPE: Patent
LANGUAGE: German
OTHER SOURCE: WPI: 1998-263284 [24]
AN 1998-07085 BIOTECHDS
AB Human colon carcinoma cell lines showing stable expression of **heat shock protein-72** (**hsp72**) of over 82% or under 20%, but having identical expression patterns on the cell surface of major histocompatibility complex and cell adhesion molecules are new. The preferred cells are derived from the CX2 or HT29 cell lines, and have over 90% or less than 10% **hsp72** expression. Most preferred lines CX+, with preferably over 90% expression, and CX-with preferably less than 10% expression are deposited as DSM ACC 2287 and 2288, respectively. These cells also have uniform

expression patterns of the intracellular, neural and vascular cellular adhesion molecules. A human carcinoma cell line expressing **hsp72** on its surface is sorted into 2 sublines with over 80% and under 20% expression, using appropriate antibodies. The expression of surface **hsp72** is closely correlated with sensitivity to lysis by natural killer (**NK**) **cells**, indicating that no heat-inducible factor other than **hsp72** is required for recognition by **NK cells**. The cells lines are used to investigate the function of **hsp72** in the development and treatment of tumors. **Hsp72** can by used to stimulate **NK cells**. (20pp)

L11 ANSWER 6 OF 20 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1998112813 MEDLINE
DOCUMENT NUMBER: 98112813 PubMed ID: 9446574
TITLE: Characterization and biological significance of immunosuppressive peptide D2702.75-84(E --> V) binding protein. Isolation of heme oxygenase-1.
AUTHOR: Iyer S; Woo J; Cornejo M C; Gao L; McCoubrey W; Maines M; Buelow R
CORPORATE SOURCE: SangStat Medical Corporation, Menlo Park, California 94025, USA.
CONTRACT NUMBER: ES03968 (NIEHS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1998 Jan 30)** 273 (5) 2692-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980306
Last Updated on STN: 19980306
Entered Medline: 19980223

AB This is the first report on peptidic inhibitors of heme oxygenase. Such peptides were originally developed from the immunomodulatory peptide 2702.75-84 which corresponds to amino acid residues 75 to 84 of the alpha1-helix of HLA-B2702 (2702.75-84) and has been shown to be immunosuppressive in vitro and in vivo. In vitro, 2702.75-84 inhibited cytotoxic T- and **natural killer cell**-mediated target cell lysis, and in vivo peptide therapy resulted in prolongation of heart and skin allograft survival in mice. The peptide was also shown to bind to **heat shock protein 70**. However, D-enantiomers of 2702.75-84 and derivatives thereof, while still being immunosuppressive, did not bind to **heat shock protein 70**. This study was designed to identify proteins binding to peptide D2702.75-84(E --> V) (rvnlrialry) consisting of D-amino acids. Compared with 2702.75-84 (RENLRIALRY), glutamic acid residue 76 (E) was replaced with valine (V). Affinity chromatography using immobilized D2702.75-84(E --> V) and mouse and human cell extracts, resulted in the isolation of heme oxygenase-1 (HO-1). Peptide D2702.75-84 inhibited HO activity in vitro in a dose dependent manner. Similar to what has been observed with other inhibitors of HO, administration of peptide into mice resulted in an up-regulation of HO-1 mRNA and protein, as well as enzyme activity in liver, spleen and kidney. Other peptides derived from 2702.75-84 with similar immunomodulatory activity displayed similar effects. In contrast, inactive derivatives of 2702.75-84 had no effect on HO activity. Therefore, the immunosuppressive effects of the described immunomodulatory peptides are similar to those of cobalt-protoporphyrin, a known up-regulator of HO-1. Our results suggest that HO-1 modulation may be a novel mechanism of immunomodulation.

L11 ANSWER 7 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:296438 BIOSIS
DOCUMENT NUMBER: PREV199800296438

TITLE: The role of heat shock proteins in the stimulation of an immune response.
AUTHOR(S): Multhoff, Gabriele (1); Botzler, Claus; Issels, Rolf
CORPORATE SOURCE: (1) GSF-Inst. Clin. Hematol., Marchioninistr. 25, D-81377 Munich Germany
SOURCE: Biological Chemistry, **(March, 1998)** Vol. 379, No. 3, pp. 295-300.
ISSN: 1431-6730.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB Heat shock proteins (HSP) have been defined as immunodominant, although most of them are highly conserved and ubiquitously distributed. Members of the 60, 70 and 90 kDa HSP families are involved in important aspects of viral and bacterial infections, in autoimmune diseases and in cancer immunity. HSP act as immunological target structures either by themselves because of an unusual expression pattern, or they are carrier proteins for immunogenic peptides. In addition to a classical major histocompatibility complex (MHC) restricted T cell response, a major contribution in the recognition of heat shock proteins has been shown for non-MHC restricted effector cells including gamma/delta TcR positive T lymphocytes and natural killer **(NK) cells**.

L11 ANSWER 8 OF 20 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999150938 MEDLINE
DOCUMENT NUMBER: 99150938 PubMed ID: 10026876
TITLE: Heat shock protein (**HSP72**) surface expression enhances the lysis of a human renal cell carcinoma by IL-2 stimulated **NK cells**.
AUTHOR: Roigas J; Wallen E S; Loening S A; Moseley P L
CORPORATE SOURCE: Department of Urology, Charite Medical School, Humboldt University of Berlin, Germany.. roigas@rz.charite.hu-berlin.de
SOURCE: ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, **(1998)** 451 225-9.
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990326
Last Updated on STN: 19990326
Entered Medline: 19990318

L11 ANSWER 9 OF 20 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998244576 MEDLINE
DOCUMENT NUMBER: 98244576 PubMed ID: 9585177
TITLE: Definition of extracellular localized epitopes of **Hsp70** involved in an NK immune response.
AUTHOR: Botzler C; Li G; Issels R D; Multhoff G
CORPORATE SOURCE: GSF-Institute of Clinical Hematology and Klinikum Grosshadern, Med. Klinik III, Munich, Germany.
SOURCE: CELL STRESS AND CHAPERONES, **(1998 Mar)** 3 (1) 6-11.
Journal code: 9610925. ISSN: 1355-8145.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980625
Last Updated on STN: 19980625
Entered Medline: 19980617
AB In order to define extracellular localized epitopes of **Hsp70** on human tumor cells which are accessible to the immune system, six

commercially available **Hsp70**-specific monoclonal antibodies (mAb) with different recognition sites were examined by immunological approaches. The recognition pattern of these antibodies was analyzed on purified recombinant **Hsp70** proteins (rHsp70, Hsc70, DnaK), on lysates of **Hsp70**-expressing colon carcinoma cells (CX+) and on lysates of M21 rat-1 cells that overexpress human **Hsp70** or **Hsp70** fragments: ABgl (del 120-428) consisting of the C-terminal part and ASma (del 438-618) consisting of the N-terminal part of human **Hsp70**. All antibodies reacted equally well with rHsp70 and cytoplasmic **Hsp70** derived from human tumor cells or M21 rat-1 cells. Only one antibody (MA3-007; **Hsp70**, Hsc70) detects a region localized within the ATPase domain of **Hsp70** (amino acid 122-264) and reacts positively with the C-terminal deletion mutant ASma. All other antibodies, including RPN1197 are directed against the C-terminal peptide binding domain of **Hsp70** and react positively with the N-terminal deletion mutant ABgl. Although all six antibodies detect full-length **Hsp70** protein, derived from plasma membrane fractions of CX+ tumor cells, cell surface expressed **Hsp70** on viable CX+ tumor cells, as determined by flowcytometry, is only recognized with the antibodies MA3-006 (**Hsp70**, Hsc70; 504-617), MA3-009 (**Hsp70**; 504-617) and RPN1197 (**Hsp70**). An estimation of the ratio of membrane-bound to cytoplasmic **Hsp70** molecules revealed that 15-20% of total **Hsp70** molecules are expressed on the plasma membrane. This tumor-selective cell surface expression of **Hsp70** correlates with an increased sensitivity to lysis mediated by non-MHC restricted natural killer (**NK**) **cells**. We demonstrate that only antibodies directed against membrane-bound **Hsp70** (MA3-006, MA3-009, RPN1197) inhibit NK-killing activity against **Hsp70**-expressing tumor cells. Taken together our data indicate that at least the C-terminal region 504-617, that contains at least one single alpha-helix (amino acid 512-536), has to be localized extracellularly and might be of importance for an NK-mediated anti-tumor immune response.

L11 ANSWER 10 OF 20 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97272152 MEDLINE
DOCUMENT NUMBER: 97272152 PubMed ID: 9126997
TITLE: **Heat shock protein 72** on tumor cells: a recognition structure for **natural killer cells**.
AUTHOR: Multhoff G; Botzler C; Jennen L; Schmidt J; Ellwart J; Issels R
CORPORATE SOURCE: Institute for Clinical Hematology, National Research Center for Environment and Health, Munich, Germany.. Multhoff@GSF.DE
SOURCE: JOURNAL OF IMMUNOLOGY, **(1997 May 1)** 158 (9) 4341-50.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970602
Last Updated on STN: 19970602
Entered Medline: 19970519

AB Evidence is accumulating that members of the **heat shock protein 70** (**HSP70**) family are found on the cell surface of certain tumor cells where they elicit a strong antitumor immune response. We demonstrated that **HSP72**, the major heat-inducible form of the **HSP70** group, is located on the cell surface of approximately 60% of the human colon carcinoma cells CX2 with two different mAbs by indirect immunofluorescence, by electron microscopy, and by selective cell surface biotinylation. In an effort to analyze the role of **HSP72** cell surface expression as a tumor-specific

recognition structure within an "autologous" tumor system, the CX2 cells were separated into a stably **HSP72** high expressing (CX+: >90%) and a stably **HSP72** low expressing (CX-: <20%) subline. The expression "autologous" was written in parentheses to indicate that the colon carcinoma sublines CX+ and CX- derived from the original CX2 tumor cell line differ with respect to the cell surface expression pattern of **HSP72**, whereas they exhibit an identical cell surface expression pattern of MHC and cellular adhesion molecules (e.g., intercellular cellular adhesion molecule, neural cellular adhesion molecule, vascular cellular adhesion molecule). Within this "autologous" tumor cell system, we demonstrate that the sensitivity to lysis mediated by adherent non-MHC-restricted effector cells correlates ($p < 0.05$) with the amount of **HSP72** that is expressed on the cell surface. Blocking studies using an **HSP72**-specific mAb revealed that **HSP72** might act in an MHC-unrestricted manner as a tumor-specific recognition structure for a distinct **NK cell** population.

L11 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:159557 CAPLUS
TITLE: Detection of **hsp70** on tumor cells.
AUTHOR(S): Galluzzo, Dominick; Fisher, Matthew; Repasky, Elizabeth
CORPORATE SOURCE: Department Chemistry, Saint Vincent College, Latrobe, PA, 15650, USA
SOURCE: Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (**1997**), CHED-265. American Chemical Society: Washington, D. C. CODEN: 64AOAA
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Fever-range whole body hyperthermia (FR-WBH) has been used successfully in the clinic as an adjunct to the more conventional means of cancer therapy. Recent unpublished results have shown that a FR-WBH treatment promotes an increase in apoptosis of tumor cells, and that natural killer (**NK**) **cells** play a key role in inducing the apoptosis. Exactly why this **NK cell**-mediated response occurs is still unknown. One possible explanation is that the hyperthermia may cause an increased expression of **hsp70** on the tumor cell surface. In an attempt to link the tumor cell surface expression of **hsp70** to the increase in apoptosis, a modified ELISA technique was developed, utilizing two antibodies: murine anti-**hsp70**, which binds directly to the **hsp70**, and goat anti-mouse conjugated with rhodamine, which binds directly to the murine anti-**hsp70**. Fluorescence measurements are then used as an indirect measurement of **hsp70** levels. This technique should be useful in detg. whether or not the levels of tumor cell surface expression of **hsp70** can be correlated with the **NK cell**-mediated increase in apoptosis of the tumor cell following a FR-WBH treatment.

L11 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:128116 CAPLUS
DOCUMENT NUMBER: 126:169815
TITLE: **Heat shock protein 72 (HSP72)**, a hyperthermia-inducible immunogenic determinant on leukemic K562 and Ewing's sarcoma cells
AUTHOR(S): Multhoff, G.
CORPORATE SOURCE: Inst. Klinische Haematologie, Munich, 81377, Germany
SOURCE: International Journal of Hyperthermia (**1997**), 13(1), 39-48 CODEN: IJHYEQ; ISSN: 0265-6736
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Following non-lethal heat stress (41.cntdot.7.degree.C) and a recover

period at 37.degree.Cm the inducible 72 kDa HSP (**HSP72**) is detectable selectively on the cell surface of human Ewing's Sarcoma (ES) and of leukemic K562 cells but not on EBV transformed B cells (B-LCL) which we generated from PBL of healthy human volunteers. The **HSP72** expression was measured by flow-cytometric anal. using a monoclonal antibody (moAb) that specifically recognizes **HSP72**, the inducible form of the **HSP70** group. The major histocompatibility complex (MHC) class I expression, detected with the moAb W6/32 was not affected by non-lethal heat exposure and a recovery period at 37.degree.C for 12 h: ES cells express MHC class I mols. on about 80% of the cells; K562 cells exhibited no MHC class I expression neither before nor after heat shock. Inhibition of RNA-(actinomycin D) or protein-synthesis (cycloheximide) prior to heat treatment completely inhibits the expression of **HSP72** on the cell surface of both tumor cells, thus indicating that de novo protein synthesis is required for **HSP72** cell surface expression. Since, apart from **HSP72**, protein synthesis in general is down-modulated by heat shock we speculate that **HSP72** mols. that are expressed on the cell surface of tumor cells might be recruited from newly synthesized proteins. The heat-inducible **HSP72** cell surface expression on tumor cells could be correlated with an increased sensitivity of leukemic and sarcoma cells to lysis mediated by NK effector cells. The results of cold target inhibition assays revealed that histol. different tumor cells (sarcoma and leukemic cells) that we exposed to non-lethal temps. have to share a similar if not identical **HSP72** immunogenic determinant.

L11 ANSWER 13 OF 20 CANCERLIT
ACCESSION NUMBER: 96649912 CANCERLIT
DOCUMENT NUMBER: 96649912
TITLE: IL-12 induced enhancement of MHC class I antigen expression on cancer cells (Meeting abstract).
AUTHOR: Suzuki S; Umezu Y; Abe Y; Kobayashi S; Satoh J; Saijo Y; Uchiyama B; Satoh K; Nukiwa T
CORPORATE SOURCE: Respiratory Oncology and Molecular Medicine, Inst. of Development, Aging and Cancer, Tohoku Univ., Sendai 980-77 Japan.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1996)** 37 A3036.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19970509
Last Updated on STN: 19970509

AB IL-12 was discovered as a potent cytokine which stimulated natural killer (**NK**) **cells** and matured cytotoxic T lymphocytes (CTL). IL-12 provides various immunological modulations. We investigated whether expressions of MHC Class I antigen, Class II antigen and **heat shock protein 70** antigen (**Hsp70**) concerning tumor antigen presentation were modulated on lung cancer cells (SBC-3; small cell line and 28-1C1; large cell line) and squamous carcinoma cells of oral cavity (UTC-8) when these cells were cultured with IL-12. We showed that expressions of MHC Class I antigen on all these cancer cells augmented about 3-10 fold when SBC-3, 28-1C1 and UTC-8 cells were cultured with IL-12 (100 units/ml) but expressions of MHC Class II and **Hsp70** antigens were not enhanced. We also found out that the expression of MHC Class I antigen raised 3-5 fold on SBC-3 cells and UTC-8 cells in which IL-12 cDNAs were transduced. These results suggest that IL-12 may provide the possibility to elicit well-recognition of tumors antigen through IL-12-enhanced expression of MHC Class I antigen followed by potent cytotoxicity and the tumor killing activities of **NK cell** and CTL.

L11 ANSWER 14 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

ACCESSION NUMBER: 1996:158870 BIOSIS
DOCUMENT NUMBER: PREV199698731005
TITLE: Noncytotoxic alkyl-lysophospholipid treatment increases sensitivity of leukemic K562 cells to lysis by natural killer (**NK**) **cells**.
AUTHOR(S): Botzler, Claus; Kolb, Hans-Jochem; Issels, Rolf D.; Multhoff, Gabriele
CORPORATE SOURCE: GSF-Inst. Klinische Haematologie, Marchioninistr. 25, D-81377 Munich Germany
SOURCE: International Journal of Cancer, (1996) Vol. 65, No. 5, pp. 633-638.
ISSN: 0020-7136.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Alkyl-lysophospholipids (ALP) are a group of anti-cancer compounds that have previously been shown to have the unique feature of being selectively toxic to neoplastic tissues. Because alkyl-lysophospholipids target the cell membrane as their site of action, our aim was to analyse the immunological effects of a nonlethal ALP treatment on leukemic K562 cells. In this in vitro study we used ET-18-OCH-3, one of the most potent ALP derivatives, at different concentrations ranging from 25 up to 100 mu-g/ml. By measurement of cell viability and of apoptosis, we determined a concentration of 25 mu-g/ml ET-18-OCH-3 and an incubation period of 2 hr as nonlethal for K562 cells; higher concentrations markedly reduced cell viability and led to induction of apoptosis. Similar to the effects induced by nonlethal heat shock, a nontoxic ET-18-OCH-3 treatment led to a significant increase in the sensitivity of K562 cells to lysis by interleukin-2 (IL-2) stimulated natural killer (**NK**) **cells**. With respect to these results, we investigated the influence of nonlethal ALP treatment on the cell surface expression patterns and compared it to the results obtained with nonlethal heat shock. ALP treatment does not induce major histocompatibility complex (MHC) expression; however, a significant increase in the cell surface expression of **HSP72** was shown by immunoblot analysis of membrane lysates of either untreated or ET-18-OCH-3 treated K562 cells. The increased sensitivity of ET-18-OCH-3 treated K562 cells to lysis by **NK cells** could be correlated with the elevated cell surface expression of **HSP72**.

L11 ANSWER 15 OF 20 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 97157087 MEDLINE
DOCUMENT NUMBER: 97157087 PubMed ID: 9003468
TITLE: **Heat-shock protein 72** cell-surface expression on human lung carcinoma cells in associated with an increased sensitivity to lysis mediated by adherent **natural killer cells**.
AUTHOR: Botzler C; Issels R; Multhoff G
CORPORATE SOURCE: GSF-National Research Centre for Environment and Health, Institute of Clinical Hematology, Munich, Germany.
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, **(1996 Dec)** 43 (4) 226-30.
Journal code: 8605732. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 19970305
Entered Medline: 19970219

AB The cell-surface expression patterns of major histocompatibility complex (MHC) class I, class II and **heat-shock protein 72** (**HSP72**) molecules were measured on human lung (LX-1)

and mammary (MX-1) carcinoma cells. No major differences were found in the MHC cell-surface expression pattern of both cell lines. However, they differ significantly in their capacity to express **HSP72** on their cell surface. Under physiological conditions LX-1 cells express **HSP72** molecules on more than 90% of the cells, whereas MX-1 cells exhibit no significant **HSP72** cell-surface expression (less than 5%). These expression patterns remained stable in all further cell passages tested. The sensitivity to lysis mediated by an interleukin-2 (IL-2)-stimulated, adherent natural killer (**NK**) **cell** population could be correlated with the amount of cell-surface-expressed **HSP72** molecules. By antibody-blocking studies, using **HSP72** -specific monoclonal antibody (mAb), a strong inhibition of lysis was only found with LX-1 cells but not with MX-1 cells. In contrast to the cell-surface expression, the cytoplasmic amount of **HSP72** in MX-1 cells was twice as high compared to LX-1 cells under physiological conditions. After nonlethal heat-shock the rate of induction and the total cytoplasmic amounts of **HSP72** were comparable in both cell lines. The clonogenic cell viability of LX-1 cells after incubation at temperatures ranging from 41 degrees C to 44 degrees C was significantly elevated compared to that of MX-1 cells. In conclusion we state the following: (i) **HSP72** cell-surface expression on human carcinoma cells is independent of the cytoplasmic amount of **HSP72**; (ii) the cell-surface expression of **HSP72** is associated with an increased sensitivity of tumor cells to lysis mediated by an IL-2-stimulated, adherent **NK cell** population; (iii) thermoresistance is not related to the cytoplasmic **HSP72** level but might be related to the amount of **HSP72** expressed on the cell surface.

L11 ANSWER 16 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:192406 BIOSIS
DOCUMENT NUMBER: PREV199799491609
TITLE: Does the nuclear co-association of **heat shock protein 70**, c.myc and p53 might be one of the mechanisms of tumor escape from immunocompetent cells in cervical carcinoma.
AUTHOR(S): Abd El All, H.; Rey, A. (1); Duvillard, P. (1)
CORPORATE SOURCE: (1) Inst. Gustave-Roussy, Villejuif France
SOURCE: Pathology International, (1996) Vol. 46, No. SUPPL. 1, pp. 175.
Meeting Info.: XXI International Congress of the International Academy of Pathology and 12th World Congress of Academic and Environmental Pathology Budapest, Hungary October 20-25, 1996
ISSN: 1320-5463.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L11 ANSWER 17 OF 20 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 95359435 MEDLINE
DOCUMENT NUMBER: 95359435 PubMed ID: 7632945
TITLE: CD3- large granular lymphocytes recognize a heat-inducible immunogenic determinant associated with the 72-kD heat shock protein on human sarcoma cells.
AUTHOR: Multhoff G; Botzler C; Wiesnet M; Eissner G; Issels R
CORPORATE SOURCE: GSF-Institut fur Klinische Hamatologie, Munchen, Germany.
SOURCE: BLOOD, **(1995 Aug 15)** 86 (4) 1374-82.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950921
Last Updated on STN: 19970203

Entered Medline: 19950914

AB Traditionally, heat shock proteins (HSPs) are believed to be located intracellularly, where they perform a variety of chaperoning functions. Recently, evidence has accumulated that some tumor cells express HSPs on the cell surface. The present study confirms this finding and correlates **HSP72** cell surface expression, induced by nonlethal heat shock, with an increased sensitivity to interleukin-2-stimulated CD3-natural killer (**NK**) **cells**. After nonlethal heat shock, a monoclonal antibody directed against the major heat-inducible 72-kD HSP (**HSP72**) stains the cell surface of sarcoma cells (ie, Ewing's sarcoma cells or osteosarcoma cells) but not that of normal cells (ie, peripheral blood lymphocytes, fibroblasts, phytohemagglutin-stimulated blasts, B-lymphoblastoid cell lines) or of mammary carcinoma cell line MX-1 carcinoma cells. In this study, we show for the first time a correlation of **HSP72** cell surface expression with an increased susceptibility to lysis by NK effector cells. This finding is supported by the following points: (1) HLA-disparate effector cells show similar, elevated lysis of **HSP72**+ heat-treated sarcoma cells; (2) CD(3-) **NK cells**, but not CD3+ cytotoxic T lymphocytes, are responsible for the recognition of heat-shocked sarcoma cells; (3) by antibody-blocking studies, an immunogenic **HSP72** determinant, which is expressed selectively on the cell surface of heat-treated sarcoma cells could be correlated with NK recognition; (4) the reported phenomenon is independent of a heat-induced, transient downregulation of major histocompatibility complex (MHC) class-I expression; and (5) blocking of MHC class-I-restricted recognition, using either MHC class-I-specific monoclonal antibody W6/32 on the target cells or alpha/beta T-cell receptor monoclonal antibody WT31 on effector cells, also has no inhibitory effect on the lysis of **HSP72**+ tumor cells. Finally, our in vitro data might have further clinical implications with respect to **HSP72** as a stress-inducible, sarcoma-specific NK recognition structure.

L11 ANSWER 18 OF 20 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:383492 BIOSIS
DOCUMENT NUMBER: PREV199598397792
TITLE: A heat inducible **heat shock protein 72** (**HSP72**) associated immunogenic determinant acts as a tumor specific recognition structure for **NK cells**.
AUTHOR(S): Botzler, C.; Multhoff, G.; Wiesnet, M.; Wilmanns, W.; Issels, R. D.
CORPORATE SOURCE: GSF - Inst. Klin. Haematol., Munich Germany
SOURCE: 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 488. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 19 OF 20 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 93171610 MEDLINE
DOCUMENT NUMBER: 93171610 PubMed ID: 8436820
TITLE: Characterization of an unusual cell type (CD4+ CD3-) expanded by helminth infection and related to the parasite stress response.
AUTHOR: Estes D M; Turaga P S; Sievers K M; Teale J M
CORPORATE SOURCE: University of Texas Health Science Center, Department of Microbiology, San Antonio 78284-7758.
CONTRACT NUMBER: AI 19896 (NIAID)
AI 20313 (NIAID)

AI 27994 (NIAID)
SOURCE: JOURNAL OF IMMUNOLOGY, **(1993 Mar 1)** 150 (5) 1846-56.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 19930402
Last Updated on STN: 19930402
Entered Medline: 19930324

AB Mice infected with the parasite Mesocestoides corti develop hypergammaglobulinemia, hepatomegaly, and splenomegaly. The immune response to M. corti infection is directed, in part, at molecules secreted by the organism. Two of these molecules have been shown to be **hsp70** and hsp60 homologues. In this study it was found that incubation of splenocytes from infected animals with M. corti-secreted molecules or the isolated M. corti **hsp70** results in the expansion of an unusual cell type with the morphology of large granular lymphocytes. The cell lines express Thy-1, CD4 (low), and CD45RB but lack TCR alpha beta, TCR gamma delta, CD3, CD8, and slg. The lack of a TCR suggested **NK cells**, but no cytolytic activity could be detected. In addition, the cell lines constitutively produce IL-6 and can be induced to express IL-2, but not IL-4, IL-5, or IFN-gamma. Given the phenotype of these cells, it is possible that they represent T lineage precursors or some type of effector cells. Notably, CD3- CD4+ cells appear to be expanded in the spleens and livers of M. corti-infected animals, suggesting an important role in infection. Moreover, the selective growth of this cell type with M. corti **hsp70** suggests that the outgrowth and in vivo expansion of these cells may be related to the stress response of the parasite.

L11 ANSWER 20 OF 20 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 91100758 MEDLINE
DOCUMENT NUMBER: 91100758 PubMed ID: 1987275
TITLE: Cellular and subcellular distribution of PBP72/74, a peptide-binding protein that plays a role in antigen processing.
AUTHOR: VanBuskirk A M; DeNagel D C; Guagliardi L E; Brodsky F M; Pierce S K
CORPORATE SOURCE: Department of Biochemistry, Molecular Biology and Cell Biology, Northwestern University, Evanston, IL 60208.
CONTRACT NUMBER: AI-18939 (NIAID)
AI-23767 (NIAID)
AI-27957 (NIAID)
+
SOURCE: JOURNAL OF IMMUNOLOGY, **(1991 Jan 15)** 146 (2) 500-6.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199102
ENTRY DATE: Entered STN: 19910329
Last Updated on STN: 19910329
Entered Medline: 19910219

AB A 72/74-kDa peptide binding protein (PBP72/74) was previously described which plays a role in the processing and/or presentation of Ag, possibly by facilitating the association of processed Ag with the MHC class II molecules. PBP72/74 was recently shown to be related to the 70-kDa family of heat shock proteins (**hsp70**), whose members show the general characteristic of binding to denatured or inappropriately folded proteins. Here we describe the cellular and subcellular distribution of PBP72/74. By

flow cytometry with PBP72/74-specific rabbit antisera, PBP72/74 is detected on the surfaces of mouse Ig+ B cells and MAC-1+ macrophages. PBP72/74 74 was not detected on the surfaces of Thy-1+ T cells or NK1.1+ **NK cells**. The cell surface expression of PBP72/74 does not require MHC class II expression. Indeed, the Ia- variant B cell lymphoma cell line, M12.C3, expresses PBP72/74 at levels equivalent to that of the Ia+ parent cell line, M12.4.1, from which it was derived. Furthermore, the fibroblast L cell line, DAP.3, shows no cell surface expression of PBP72/74, nor do DAP.3 lines transfected with and expressing genes encoding the alpha- and beta-chain of the I-Ad and I-Ed molecules. Moreover, treatment of B cells with either IL-4 or LPS, which increases Ia expression severalfold, does not affect PBP72/74 expression. Thus, PBP72/74 cell surface expression appears to be a property of B cells and macrophages, independent of Ia expression. In addition, the B cell surface expression of PBP72/74 is not altered by stress in the form of heat shock. Thus, PBP72/74 appears to be a constitutive noninducible member of the **hsp70** family. By immunoelectron microscopy, PBP72/74 is detected in approximately 36% of early endocytic vesicles into which surface Ig is internalized after binding to anti-Ig antibodies. This compartment was previously shown to contain class II en route to the cell surface associated with invariant chain and the proteases cathepsin B and D and is suggested to be a subcellular site of antigen processing. PBP72/74 is also found associated with the plasma membrane, endoplasmic reticulum, and membranes proximal to the Golgi stacks. The cellular and subcellular distribution of PBP72/74 is consistent with its playing a role in the processing of presentation of Ag with the MHC class II molecules.

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=> d history

     (FILE 'HOME' ENTERED AT 17:11:13 ON 15 DEC 2002)

     FILE 'MEDLINE, BIOSIS, CANCERLIT, LIFESCI, BIOTECHDS, CAPLUS' ENTERED AT
     17:11:29 ON 15 DEC 2002
L1         74620 S HSP## OR (HEAT(W)SHOCK(W)(PROTEIN# OR PEPTIDE#))
L2         83305 S (NK OR (NATURAL(W)KILLER))(W)CELL#
L3           298 S L1 AND L2
L4            92 S L3 AND ACTIVAT?
L5            57 S L4 AND PY<2000
L6            24 DUP REM L5 (33 DUPLICATES REMOVED)
L7         26787 S HSP7# OR (HEAT(W)SHOCK(W)PROTEIN(W)7#)
L8           128 S L7 AND L2
L9            68 S L8 AND PY<2000
L10           50 S L9 NOT L5
L11           20 DUP REM L10 (30 DUPLICATES REMOVED)

=> log h
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    102.96     103.17

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STN INTERNATIONAL SESSION SUSPENDED AT 17:49:11 ON 15 DEC 2002
Connection closed by remote host
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L11 ANSWER 9 OF 20 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998244576 MEDLINE
DOCUMENT NUMBER: 98244576 PubMed ID: 9585177
TITLE: Definition of extracellular localized epitopes of **Hsp70** involved in an NK immune response.
AUTHOR: Botzler C; Li G; Issels R D; Multhoff G
CORPORATE SOURCE: GSF-Institute of Clinical Hematology and Klinikum Grosshadern, Med. Klinik III, Munich, Germany.
SOURCE: CELL STRESS AND CHAPERONES, **(1998 Mar)** 3 (1) 6-11.
Journal code: 9610925. ISSN: 1355-8145.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980625
Last Updated on STN: 19980625
Entered Medline: 19980617

AB In order to define extracellular localized epitopes of **Hsp70** on human tumor cells which are accessible to the immune system, six commercially available **Hsp70**-specific monoclonal antibodies (mAb) with different recognition sites were examined by immunological approaches. The recognition pattern of these antibodies was analyzed on purified recombinant **Hsp70** proteins (rHsp70, Hsc70, DnaK), on lysates of **Hsp70**-expressing colon carcinoma cells (CX+) and on lysates of M21 rat-1 cells that overexpress human **Hsp70** or **Hsp70** fragments: ABgl (del 120-428) consisting of the C-terminal part and ASma (del 438-618) consisting of the N-terminal part of human **Hsp70**. All antibodies reacted equally well with rHsp70 and cytoplasmic **Hsp70** derived from human tumor cells or M21 rat-1 cells. Only one antibody (MA3-007; **Hsp70**, Hsc70) detects a region localized within the ATPase domain of **Hsp70** (amino acid 122-264) and reacts positively with the C-terminal deletion mutant ASma. All other antibodies, including RPN1197 are directed against the C-terminal peptide binding domain of **Hsp70** and react positively with the N-terminal deletion mutant ABgl. Although all six antibodies detect full-length **Hsp70** protein, derived from plasma membrane fractions of CX+ tumor cells, cell surface expressed **Hsp70** on viable CX+ tumor cells, as determined by flowcytometry, is only recognized with the antibodies MA3-006 (**Hsp70**, Hsc70; 504-617), MA3-009 (**Hsp70**; 504-617) and RPN1197 (**Hsp70**). An estimation of the ratio of membrane-bound to cytoplasmic **Hsp70** molecules revealed that 15-20% of total **Hsp70** molecules are expressed on the plasma membrane. This tumor-selective cell surface expression of **Hsp70** correlates with an increased sensitivity to lysis mediated by non-MHC restricted natural killer (**NK**) **cells**. We demonstrate that only antibodies directed against membrane-bound **Hsp70** (MA3-006, MA3-009, RPN1197) inhibit NK-killing activity against **Hsp70**-expressing tumor cells. Taken together our data indicate that at least the C-terminal region 504-617, that contains at least one single alpha-helix (amino acid 512-536), has to be localized extracellularly and might be of importance for an NK-mediated anti-tumor immune response.